REMARKS

Upon entry of the amendment, claims 13-29, 34, 36, and 42-51 will be pending in the application, claims 30-33, 35 and 37-41 having been canceled and new claims 43-51 added. Claims 13, 16-18, 20, 21, 24, 26-29, 34, 36 and 42 have been amended. Support for the amendments and the new claims can be found in the specification and claims as originally filed. For example, support for amended claims 13, 36, and 42, and new claims 50 and 51 can be found, *e.g.*, at page 3, lines 7, 13, 18-19, and 29-30; page 4, lines 1-2 and 19-22; and page 8, lines 24-27. Support for amended claim 34 can be found, *e.g.*, at page 3, lines 7-9 and 18-19. Support for new claim 43 can be found, *e.g.*, at page 6, line 12. Support for new claim 44 can be found, *e.g.*, at page 6, lines 19-21. Support for new claims 45-47 can be found, *e.g.*, at page 6, lines 24-28. Support for new claim 48 can be found, *e.g.*, at page 8, lines 24-29, and support for new claim 49 can be found, *e.g.*, at page 3, lines 7 and 13; page 4, lines 7-10; and page 8, lines 24-27. No new matter is added by the amendment.

Applicant thanks the Examiner for returning an initialed copy of the form PTO-1449 that was submitted on September 19, 2003. Applicant notes, however, that the Examiner also enclosed a second initialed form PTO-1449 that apparently applies to a different and unrelated case. The inventor in the unrelated case is Alicia Peterson, not Tommy Ekstrom, the named inventor in the current application.

Double Patenting

Claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 were provisionally rejected on the ground of nonstatutory double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 of the parent copending U.S. application no. 09/367,950. Claims 30-33, 35, and 38 have been canceled, and therefore the rejection of these claims is moot.

The parent copending application is under appeal at the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences. If the claims in the parent application are still pending, or are issued, at the time Applicant receives an indication from the present Examiner

that the claims in the current application are otherwise in condition for allowance, Applicant will file a terminal disclaimer if such action is still deemed to be appropriate.

35 U.S.C. § 112, first paragraph

Claims 13-42 were rejected under 35 U.S.C. 112, first paragraph, because, according to the Examiner, the specification, "while being enabling for the treatment of asthma, does not reasonably provide enablement for the prevention of asthma." Office Action at page 4. Claims 30-33, 35, and 37-41 have been canceled, so the rejection as applied to these claims is moot.

Applicant does not concede that the claims lack enablement insofar as they are directed to the prevention of asthma. However, for the purpose of expediting prosecution and for placing the claims in condition for allowance, Applicant has removed the word "prevention" from the claims. In view of the amendment, Applicant requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

It is noted that page 5 of the Office Action states that "[t]he instant claims are drawn to a method of eliminating an individual's tobacco or nicotine usage habit." It appears the Examiner may have confused the present case with another. The present claims are clearly directed to methods of treating asthma.

35 U.S.C. § 103

Claims 13-15, 17, 18, and 20-42 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Carling *et al.* (WO 93/11773). Claims 30-33, 35, and 37-41 have been canceled, so the rejection as applied to these claims is moot. Applicant also notes that the claims as amended are no longer directed to a method comprising instructing a patient. Instead, the claims now are drawn to a method comprising administering the recited composition. On the chance that the Examiner will maintain the rejection, even in view of the amendment, Applicant presents the following remarks.

Applicant disagrees that the claims (whether before or after the current amendment) are obvious in view of Carling *et al*. As amended, all claims are drawn to methods of treating asthma, which methods comprise administering an effective amount of a combination of active ingredients comprising formoterol (or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt) and budesonide. (Formoterol is a bronchodilator typically used to control or relieve the overt symptoms of asthma, *i.e.*, as a "rescue" medication, while budesonide is a corticosteroid useful for reducing chronic inflammation, *i.e.*, as a prophylactic medication.) The independent claims differ in the details of administering the composition to the patient, as follows. Independent claim 13 (as amended) requires that the patient be administered (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular, as-needed basis for rescue purposes. Independent claim 36 (as amended) requires that the patient be administered (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses when the patient expects to encounter an asthma-inducing condition. Independent claim 42 (as amended) requires that the patient be administered (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses if and when the patient experiences an acute asthma attack. New independent claim 49 requires that the patient be administered (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis when needed for symptom relief. New independent claim 50 requires that the patient be administered (i) a maintenance dose of the composition on a regular basis as determined by the patient's physician, and (ii) one or more additional doses on an irregular basis when the patient determines it is needed for symptom relief or when the patient expects to encounter an asthma inducing condition, and new independent claim 51 requires that the patient be administered the composition on an irregular basis when the patient determines it is needed for symptom relief or when the patient expects to encounter an asthma inducing condition. Therefore, each of the independent claims requires that the patient be administered at least one dose that can vary in frequency from day to day, *e.g.*, from zero on a given day to multiple times on another day. Note that none of the claims requires that the irregular dose be administered

every day. Instead, the dose is administered only in response to a specified influence (*e.g.*, for rescue purposes, when the patient expects to encounter an asthma-inducing condition, when the patient experiences an acute asthma attack, or when needed for symptom relief). Further, while the "one or more additional doses," or the dose administered on an irregular basis, can be frequent or infrequent, there must be at least one such dose at some point over the course of treatment covered by the claims.

Arriving at these methods resulted from an insight by Applicant. Determination of whether and when the additional irregular doses should be administered requires decisions by the patient (or the patient's guardian), where previously the frequency of budesonide administration was always strictly limited to a maintenance dosage set by the physician (see evidence concerning that point discussed below). Applicant discovered that the budesonide/formoterol combination could be administered as both a regular maintenance dosage that does not vary with the patient's symptoms, and as additional, irregular doses according to the patient's determination of need, and that administering it in this way would greatly improve control over the patient's asthma and reduce the number of asthma attacks suffered by the patient. Applicant also discovered that this could be done without incurring in practice a substantial risk of overdose of budesonide, a potent glucocorticosteroid. These insights were nowhere in the prior art, and in fact represented a radical departure from how patients were administered budesonide-containing compositions prior to June 11, 1998, the priority date of the present application.

The Supreme Court in Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966), explained that, to reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when Applicant's invention was unknown and just before it was made. More recently, in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740-1741 (2007), the Supreme Court reaffirmed that the fact finder must identify and make explicit some reason that one of ordinary skill would have derived the claimed invention from elements taught in the art. This concept is consistent with Patent Office policy as set forth at MPEP 2141, which states that in view of all

factual information, the Examiner must make a determination whether the claimed invention "as a whole" would have been obvious to that person at the priority date.

Applicant presents evidence of nonobviousness below. Such evidence includes the teachings of Carling *et al.* itself and extrinsic evidence showing how a person of ordinary skill in the art would have interpreted Carling *et al.* at the priority filing date of the application. Applicant also explains below why there is no reason to alter the teachings of Carling *et al.* to arrive at the claimed methods, and why one of ordinary skill in the art would not have had a reasonable expectation that the claimed methods would succeed. Finally, Applicant presents surprising results, and evidence of long-felt unsatisfied need and skepticism of experts, all of which are objective evidence of non-obviousness as established by the court in Graham and which must be considered by the Examiner. In view of the totality of evidence described below, the claimed methods are not obvious in view of Carling *et al.*

Carling et al. teaches a twice daily dosing regime for treatment of asthma. Carling *et al.* discloses treatment of asthma by inhalation of a combination of formoterol and budesonide from a single inhaler. According to Carling *et al.* at page 4, lines 19-21, "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." (Emphasis added.) Similarly, page 6, lines 22-29, says, "The intended dose regimen is a twice daily administration...." Such a set, twice-daily regimen has long been, and still is today, a standard asthma treatment protocol for anti-inflammatory glucocorticosteroids such as budesonide. Commonly termed "maintenance therapy," it is intended to reduce over the long term the chronic inflammation that, if uncontrolled, can contribute to spasms of bronchoconstriction—*i.e.*, acute asthma attacks. Typically the asthma patient will also be prescribed an inhaler containing a short-acting bronchodilator for use as needed to stop an imminent or ongoing attack that occurs despite the glucocorticosteroid maintenance therapy regimen. Use of that short-acting bronchodilator is left to the discretion of the patient. In contrast, use of budesonide or other powerful glucocorticosteroids is not—or at least wasn't until the present invention. As will be clear from evidence discussed in detail

below, patients who were prescribed a budesonide-containing inhaler were warned not to take any more (or any fewer) doses from their budesonide inhaler than the two fixed doses per day prescribed by the physician for maintenance therapy. This reflects both what was perceived to be the relatively slow-acting nature of glucocorticosteroids, rendering them mostly useless in an acute attack, and the danger of systemic side effects from overdosing on glucocorticosteroids in general. While the physician had the discretion to adjust the size of the two fixed daily doses of glucocorticosteroid according to factors such as the age and weight of the patient or the severity of the patient's illness, such adjustments were solely at the discretion of the physician. The patient would not make that decision, and the number of administrations of budesonide or other glucocorticosteroid would generally remain at twice per day even if the prescribed fixed dosage per administration were changed by the physician. Evidence supporting these assertions, including statements derived from various inhaler product inserts, is discussed below.

The Examiner states that

> [t]o one of ordinary skill in the art, it would have been obvious to combine the method of Carling *et al.* and instructing the patient to inhale, on demand in any of the circumstances detailed in claims 32-49 [sic] and 41-42 because Carling *et al.* teaches that the dosages strongly depend on the severity of disease, whether mild, moderate, or sever asthma (see pg. 6, lines 27-29), and the suitable daily dosage is up to 8 inhalation (see page 7-9). *Office Action at page 10.*

Applicant notes that the claims no longer require that a patient be "instructed" to inhale the composition on demand. Instead, the claims are drawn to methods of administration.

The Examiner's reference to "up to 8 inhalation per day" appears to derive from some of Carling *et al.*'s examples of inhalers described on pages 7-9 as delivering 12 μg of formoterol and either 100 or 200 μg budesonide, combined with Carling *et al.*'s teaching on page 6, lines 24-26, that a "suitable daily dose" of formoterol is 6 to 100 μg and a "suitable daily dose" of budesonide is 50 to 4800 μg. Thus, in theory one could inhale eight "puffs" from an inhaler that delivers a combination of 12 μg formoterol and 100 or 200 μg budesonide per puff without exceeding what Carling *et al.* teaches is the upper end of the range of a suitable daily dose of formoterol (100 μg) and the upper end of the range of a suitable daily dose of budesonide

(4800 µg). The reference itself actually says nothing about the number of inhalations per administration, rather only that those inhalations should be grouped into just two administrations per day ("the intended dose regimen is a twice daily administration" (page 6, lines 22-23)) and should deliver a total daily dose within the recommended ranges. Each of the two administrations per day intended by Carling *et al.* could, in theory, involve a single "puff," or two or more "puffs"—whatever is needed to achieve the fixed daily dosage prescribed by the physician using whatever inhaler is commercially available. The mere fact that a particular inhaler delivers a dose that is less than half of a prescribed daily dose does not mean that the prescribed daily dose should be spread out into more than two administrations per day, in contravention of Carling *et al.*'s explicit teachings that the intended dose regimen is twice daily. The Office Action at page 8 cites page 4 of Carling *et al.* as saying that the formoterol/ budesonide combination provides a "rescue medicine." Carling *et al.* clearly uses this term to refer to the formoterol part of the combination, since formoterol is a bronchodilator that can be utilized to reverse immediate symptoms of bronchoconstriction, while budesonide acts more slowly to control the underlying inflammation. Carling *et al.* subsequently states that "[t]he combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." Id. at page 4, lines 19-21 (emphasis added). One of ordinary skill in the art would not read Carling *et al.* to suggest that more than two doses of the combination could be administered in any one day for at least the reasons described above (and further below), and certainly would not read Carling *et al.* to suggest that a patient should be administered a maintenance dose twice daily plus one or more additional doses as needed, as specified in the present claims.

Extrinsic evidence indicates that one of ordinary skill in the art at the filing date of the application would have agreed with Applicant's interpretation of Carling et al. As evidence that one of ordinary skill in the art of asthma therapy would have agreed with Applicant's interpretation of Carling *et al.*, Applicant submits Exhibits 1-5. The exhibits show that from a date prior to the present priority date (1998) to as late as 2003, glucocorticosteroid-containing

therapeutics were routinely prescribed for fixed-dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen. Once one understands how inhaled glucocorticosteroids such as budesonide were typically prescribed for asthma patients prior to Applicant's invention, it is apparent that Applicant's interpretation of Carling *et al.* is the one that a person of ordinary skill would have taken from this reference.

Certain sections of these Exhibits have been circled and labeled in the margin with a capital letter for ready reference.

The glucocorticosteroid budesonide is the sole active ingredient in an inhaler sold under the trademark Pulmicort® Turbuhaler® for maintenance treatment of asthma. A copy of a 1997 product insert packaged with the Pulmicort® Turbuhaler® product is submitted as Exhibit 1. Recommended starting doses and highest recommended doses for various categories of patients are set out in a table in this document (Exhibit 1, page 4, section A); each and every one of these doses is to be administered "twice daily." There is no provision for additional doses to be taken. Indeed, the section titled "Patient's Instructions for Use" on page 2 of the document (see entire bottom half of page 2) repeatedly and emphatically instructs the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether the patient is feeling better or worse on a given day.

The patient instructions concerning dosage (labeled as section B on page 2 of Exhibit 1) are quoted in their entirety below:

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler
- **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER**, unless told to do so by your doctor.

- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose. (Emphasis in original).

These instructions provide objective evidence that the paradigm for treatment of asthma with budesonide in 1997 was for a physician to prescribe a particular number of doses (generally two) per day for a patient and instruct the patient to take exactly that number of doses, no more or less. The third and last bullet points of the above instructions are particularly telling. Under no circumstances was the patient to take more doses than the specific number prescribed by the physician. Even if the patient missed a dose, the patient was not to take even a single extra dose. This is directly contrary to the Examiner's assertion that

> If the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage…The skilled artisan would have been motivated to instruct the patient to use the Carling *et al.* composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment and common asthma triggers. Office Action at the paragraph spanning pages 10-11.

Exhibit 1 also says:

> Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.…If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician. Exhibit 1, page 3, section C.

This further illustrates that the physician, and not the patient, determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms, he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief.

> "PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma." Exhibit 1, page 2, section D.
>
> "PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required." Exhibit 1, page 1, section E.
>
> "If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur." Exhibit 1, page 3, section F.
>
> "Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA [hypothalamic-pituitary-adrenal] dysfunction [a deleterious side-effect of glucocorticosteroid overdosing] may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose." Exhibit 1, page 3, section G.

These warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly in a fixed dose that is set (and carefully monitored) by the physician according to the patient's needs, but had no role in short-term relief of acute symptoms. The only medication that could be taken by the patient on an as-needed basis was a short-acting bronchodilator. The physician was explicitly directed to ensure that the patient received the lowest effective fixed dose of budesonide. Even in 1997 (four years after Carling *et al.*), administering additional doses to a patient on an as-needed basis, such as in an acute attack, was strictly forbidden. There was no evidence that taking budesonide more frequently or in larger doses than prescribed would be of any benefit to the patient, and there was a significant risk of harm.

That 1997 product insert pertains to budesonide alone, rather than a combination product. There are now at least two combination glucocorticosteroid/bronchodilator inhalation products (comparable to the combination product disclosed by Carling *et al.*) on the market for treatment of asthma. Product inserts for the two marketed products are presented as Exhibits 2 and 3. As elaborated below, for both products the physician instructs the patient to inhale a set dose, twice per day--consistent with Applicant's interpretation of Carling *et al.*

The first combination product is SYMBICORT TURBUHALER®, a budesonide/formoterol inhalation powder product similar to that disclosed by Carling *et al.* Exhibit 2 is a product insert circa 2001 for that product. It says that the "recommended dosage" is 1-2 inhalations twice daily (Exhibit 2, page 1, section A); when control of symptoms is achieved with the twice daily regimen, the physician can choose to reduce the number of inhalations to one daily (Exhibit 2, page 1, section B).

The insert instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease: "The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated." Exhibit 2, page 1, section C.

There is no suggestion anywhere in the document that the patient can choose to self-administer additional doses, beyond the twice daily regimen. To the contrary, use outside of the fixed dosage regimen is dangerous and forbidden: "If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought." Exhibit 2, page 2, section D.

Moreover, "increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy"; "patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained." Exhibit 2, page 2, section E; and page 1, section F, respectively (emphasis added).

These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the treatment protocol can be reassessed (and if necessary, adjusted) by the physician. Adjusting the dosage from day to day at the patient's discretion is nowhere contemplated.

The second combination product is the Advair Diskus® fluticasone propionate/salmeterol xinafoate inhalation powder product. This combination is prescribed for use twice per day, at a dose set by the physician. (Like budesonide, fluticasone propionate is a glucocorticosteroid, and like formoterol, salmeterol xinafoate is a beta-2 agonist.) The Patient's Instructions for Use

(March 2003) for this product, attached as Exhibit 3, emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The pertinent portion of these instructions, found on page 2 of the insert, is reproduced below:

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.
4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.
6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**

The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. Like the evidence discussed above, this evidence (from 2003) is directly contrary to the Examiner's assertions regarding what would have been "obvious" to one of ordinary skill in the art ten years earlier, in view of Carling *et al.* in 1993.

The above evidence also constitutes a "teaching away" from the claimed methods, which require administration of at least one dose as determined by the patient. The Court in KSR reaffirmed the "corollary principle that when the prior art teaches away from combining known

elements, discovery of a successful means of combining them is more likely to be nonobvious." KSR at 1740. The product literature above states, *e.g.*, "**DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises"; "PULMICORT TURBUHALER is not…indicated for rapid relief of bronchospasm or other acute episodes of asthma"; "**Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time**"; and "**DO NOT USE ADVAIR DISKUS TO RELIEVE SUDDEN ASTHMA SYMPTOMS**" (emphasis in originals). The disclosure of the product literature is in direct contradiction of, and therefore teaches away from, the claimed methods.

Clearly even as late as 2003 (long after the 1998 priority date of the present application), glucocorticosteroid-containing inhaled therapeutics were routinely prescribed solely for fixed-dosage use as maintenance therapy, and not for immediate relief of worsening symptoms. One of ordinary skill in the art of inhaled glucocorticosteroid therapy for treatment of asthma would have understood in 1998 that patients were never instructed to take inhaled glucocorticosteroids as a reliever medication, to be administered in addition to a maintenance dose. Carling *et al.* would certainly not have been read as recommending such a radical—and potentially dangerous—departure from the norm.

Further evidence concerning the proper interpretation of Carling *et al.* is provided by the publications submitted herewith as Exhibits 4 and 5. Exhibit 4 is a journal article (O'Byrne *et al.*, "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," *Am J Respir Crit Care Med* 171:129-136, 2005) discussing the positive results of a recent clinical trial studying the efficacy of Applicant's claimed method for reducing the incidence of asthma exacerbations and other asthma symptoms. Exhibit 5 (Barnes, "A Single Inhaler for Asthma?" *Am J Respir Crit Care Med* 171:95-96, 2005) is an editorial in the same journal issue. Dr. Barnes states his opinion that "the study by O'Byrne and his colleagues may lead to changes in the paradigm of asthma management…" Exhibit 5, page 95, last paragraph, emphasis added. Moreover, Dr. Barnes views the success of Applicant's treatment protocol as "remarkable," even several years after Applicant's priority date:

> The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. (page 95, col.1, last paragraph)

Dr. Barnes explains in the carryover sentence of columns 1-2 one reason why this approach was not previously contemplated: "A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then notes that this turned out not to be a problem in practice. In fact, the patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day, yet this approach was more effective in preventing exacerbations than doubling the fixed daily amount of budesonide had proven in a different study. Dr. Barnes notes that these are "surprisingly good results" (page 95, col.2, first full paragraph).

It is to be kept in mind that these statements by Dr. Barnes, including the characterization of the O'Byrne *et al.* report as including "surprisingly good results," were made in 2005, twelve years after the Carling *et al.* reference was published. In the heavily researched field of asthma treatment, if Applicant's invention had indeed been obvious from Carling *et al.*'s teachings, it would not, twelve years later, have been regarded as the radical departure from the norm implied by the Barnes editorial. As the Federal Circuit stated in Environmental Designs, Ltd. v. Union Oil Co. of Cal., 713 F.2d 693, 698 (Fed. Cir. 1998), "Expressions of disbelief by experts constitute strong evidence of nonobviousness." See also MPEP 716.05. Barnes' objective characterization of Applicant's treatment as "remarkable" and the results as "surprisingly good" certainly qualifies as strong evidence of nonobviousness.

In view of the foregoing, one would not have interpreted Carling *et al.* as teaching that additional doses of the combination therapy could be administered on an irregular basis, on demand or as needed in addition to a prescribed maintenance dose.

The Examiner has articulated no logical reason why one of ordinary skill would alter the teachings of Carling et al. to result in the claimed methods, and one of ordinary skill in the art would not have had a reasonable expectation that the claimed methods would succeed. The attached exhibits (particularly Exhibit 1) help to establish the level of ordinary skill in the art at the time of Carling *et al.* and at the filing date of Applicant's application. With this level of ordinary skill in the art in mind, Applicant turns to the question of whether the Examiner has met her burden of establishing (1) that one of ordinary skill would have had a reason to alter Carling's teachings to arrive at the presently claimed methods (KSR at 1740-1741); and (2) that one of ordinary skill in the art would have reasonably expected the claimed invention to work (Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)), both being essential elements of any *prima facie* case of obviousness. These elements are addressed in turn.

Reason to carry out the claimed methods: The Examiner's position regarding motivation is set forth at page 10 of the Office Action. Applicant understands the Examiner's position to stem from a combination of certain interpretations of Carling *et al.*, which Applicant restates as follows:

(a) the Examiner's deduction that the maximum dosage recommended by Carling *et al.* at page 6, lines 24-27, can be divided into eight separate inhalations;

(b) the Examiner's conclusion that, because the eight inhalations add up to no more than Carling *et al.*'s maximum suggested daily dose, all eight could be "safely inhaled" by a patient on any given day, at the patient's discretion; and

(c) the Examiner's view that Carling *et al.*'s statement on page 6, lines 27-29, that "[the] particular dose used will strongly depend on the patient (age, weight *etc*) and the severity of the disease (mild, moderate, severe asthma *etc*)" means that the patient should be instructed to make the determination of his/her dosage on any given day, up to a total of eight inhalations.

Applicant believes these interpretations of Carling *et al.*'s teachings do not accurately characterize how one of ordinary skill in the art of asthma treatment would have read this reference. For example, the Examiner has made the unwarranted assumption (paraphrased in

part (b) above) that every asthma patient will be able to "safely inhale" even the high end of the ranges of "suitable daily doses" set forth at page 6, lines 24-27, of Carling *et al.* (the ranges being 6-100 µg of formoterol and 50-4800 µg of budesonide). Even if Carling *et al.* hadn't gone on to explain that the "particular dose" depends "strongly" on patient-specific factors ("the particular dose used will strongly depend on the patient (age, weight, *etc*) and the severity of the disease (mild, moderate, severe asthma etc)," one of ordinary skill in the art of asthma treatment would clearly not have read Carling *et al.*'s teachings about dosage ranges as meaning all patients can safely inhale all doses up to and including the maximum. That simply is not reasonable. Young children, for example, would not be able to safely inhale the same daily dosage that a 200 lb. adult could handle. Further, the Examiner's assumption is inconsistent with the knowledge in the art that budesonide and other glucocorticosteroids are potent drugs with dangerous side effects, whose use must be carefully monitored in every patient to avoid overdosing (see evidence to that effect discussed above).

Applicant also notes that Carling *et al.'s* reference to "severity of the disease" as being one of the bases for setting the amount of the twice-daily dose of the composition does not mean that the patient should be administered more doses if his/her disease is particularly severe on a given day. It simply means that the overall level of the patient's disease is one of the factors (along with the patient's age, weight, *etc.*) the prescribing physician should take into account in setting the twice-daily dose. A patient who chronically exhibits a particularly high level of lung inflammation might logically be prescribed a larger maintenance dose of steroid than another patient with a low level of lung inflammation. Thus, this statement cannot be read as providing any reason to administer any doses in addition to the twice-daily maintenance dose. Without an articulated reason to alter Carling *et al.*'s teachings to arrive at the presently claimed methods, the obviousness rejection fails. KSR at 1741.

Expectation of Success: The statement in the Office Action that seems to communicate the Examiner's view regarding "expectation of success" is at the paragraph spanning pages 10-11:

> The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable

> expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. *Non-standard English in original.*

As Applicant understands it, the Examiner is saying that one of ordinary skill would have a reasonable expectation of successfully treating any and all asthma patients by simply handing them an inhaler containing Carling *et al.*'s formoterol /budesonide composition and telling them to inhale any amount per day that they wish, up to and including the maximum daily dose of 100 μg formoterol and 4800 μg budesonide, because that will give them "maximum benefit," whatever the level of severity of their condition. Applicant points out that Carling *et al.* warns the reader that the particular dose of the combination "will strongly depend" on patient-specific factors, factors that are not normally left to the judgment of the patient. While the quoted passage from Carling *et al.* was referring to a fixed, twice-daily dose, the same would certainly be true of any additional doses taken (or administered) each day. Further, at least with respect to the budesonide part of this composition, Applicant has provided ample evidence that one of ordinary skill in 1997 would NOT have had such a reasonable expectation of success under the scenario the Examiner believes is "obvious." In fact, the very idea would have shocked the medical establishment. (See above discussion of Exhibit 1.) This view apparently had not changed by 2001 when the formoterol/budesonide combination product was marketed with a product insert warning the user not to exceed the fixed, twice-daily dosage prescribed by the physician. (See above discussion of Exhibit 2.) Because the Examiner has not established that one of ordinary skill at the 1998 priority date would have had a reasonable expectation that the claimed methods would succeed, her *prima facie* case of obviousness must fail.

Applicant's evidence of surprising results, long-felt unsatisfied need, and skepticism of experts is objective evidence of non-obviousness. The above evidence and arguments demonstrate that the Examiner has not met her burden in making out a *prima facie* case of obviousness. Accordingly, it is unnecessary for Applicant to come forward with objective evidence to rebut the Examiner's case. However, such evidence has already been presented in

other contexts above, so Applicant will discuss it below as a further indication of the non-obviousness of the presently claimed methods. Graham. Such objective evidence must be taken into account by the Examiner. In re Soni, 54 F.3d 746 (Fed. Cir. 1995).

First, Applicant points to the objective evidence of ***surprising results*** embodied in Exhibit 4 (O'Byrne *et al.*). The authors conducted clinical trials to compare three different treatment regimens for asthma. The relevant features of the Study Design (page 130, first column) are summarized below.

In the first treatment arm (nicknamed "bud/form maintenance + relief") of the O'Byrne *et al.* study, the patients were instructed to use a budesonide/formoterol combination inhaler twice per day, every day, for maintenance, plus the same inhaler for relief of symptoms on an as-needed basis, as determined by the patient. This first treatment arm was thus instructed in accordance with the present claims.

Patients in the second treatment arm ("bud/form + SABA") were instructed to use the same budesonide/formoterol combination inhaler just twice per day, and no more: *i.e.*, for maintenance therapy only. A second inhaler containing a different drug, the short-acting bronchodilator terbutaline, was provided to the patients of this second treatment arm for use as needed for immediate relief of acute asthma symptoms. Since this second treatment arm received the budesonide/formoterol combination just twice per day, as explicitly taught by Carling *et al.*, it is representative of the closest prior art identified by the Examiner.

Patients in the third treatment arm ("bud + SABA") were instructed to use a budesonide-only inhaler just twice per day. For relief of acute symptoms, these patients used a second inhaler containing terbutaline as needed. This third treatment arm thus represents the prior art such as in the Pulmicort Turbuhaler® 1997 product insert of Exhibit 1, in which a budesonide-only inhaler was used for maintenance therapy twice per day, and the patient was instructed to use a separate bronchodilator product as needed for relief of acute symptoms (see the section labeled "T" on page 2 of Exhibit 1).

As shown in the first bar graph of Figure 1B of O'Byrne *et al.*, use of the budesonide/formoterol product as needed for relief of acute symptoms decreased the total

number of severe exacerbations (acute asthma attacks) experienced by those patients, compared to the total number experienced by patients instructed to follow either of the prior art methods. Table 2 analyzes the data in another way: only 16% of the patients who used the product for rescue purposes experienced severe exacerbations, compared to 27% or 28% of the patients in the two prior art treatment arms, respectively. Similarly striking differences were seen in many other measures described in detail in the Results section on page 130, in Figures 1 and 2, and in Table 2. In view of this article, it is irrefutable that the presently claimed method produces results that are unexpectedly better than what the prior art methods produce.

Second, Applicant notes that two additional Graham-derived categories of objective indicia of nonobviousness are embodied in the editorial by Peter J. Barnes, M.D., attached as Exhibit 5: *long felt, unsatisfied need* and *skepticism of experts*, as well as support for the *surprising results* nature of the O'Byrne *et al.* results. Dr. Barnes is an expert in the field of asthma therapies who is associated with the National Heart and Lung Institute, Imperial College, London, UK. His editorial, which is also discussed above in another context, opines as follows regarding the significance of the O'Byrne *et al.* clinical results.

Dr. Barnes begins with the following statement of long felt, unsatisfied need for an effective asthma treatment: "Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations, with considerable disruption to their daily life." Barnes goes on to discuss O'Byrne *et al.*'s findings that treatment with the combination inhaler for both maintenance and relief "markedly reduced the number of severe exacerbations…over the 1-year treatment period compared with the other treatments," and also "reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens," implying that here at last may be a way to satisfy that long felt need, at least for many patients inadequately served by prior therapies. Dr. Barnes offers his view that the O'Byrne *et al.* study "may lead to changes in the paradigm of asthma management," another indication that he believed it is at least a partial answer to the long felt need. Dr. Barnes also describes what amounts to past skepticism of experts regarding the claimed method: "A concern about this approach is that some patients might end up using the

combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then reassures the reader: "However, this was not the case, as the mean number of additional doses of combination inhaler was only one dose per day and very few patients used high doses." Finally, the editorial makes the point that the O'Byrne *et al.* findings were "remarkable" and "surprisingly good results," supporting quite literally Applicant's thesis that the present claimed methods produce surprising results compared to both the prior art Carling *et al.* method and the prior art budesonide-only method, results that could not have been predicted in view of any of this prior art.

It is clear from the Exhibits and the arguments presented above that one of ordinary skill in the art of asthma therapy at the priority date would not have interpreted Carling *et al.* as suggesting that patients should inhale one or more doses of a budesonide-containing product in addition to the regular, twice-daily maintenance therapy. The paradigm for use of budesonide-containing products dictated fixed dosage use for maintenance therapy only, not variable dosage as determined day-to-day by the patient. And certainly Carling *et al.* gave no reason to expect the surprisingly good results reported by O'Byrne *et al.*

Because the cited passage of Carling *et al.* does not teach or suggest a method of administering one of more doses of a formoterol/budesonide composition on an irregular basis, when needed, and one of ordinary skill in asthma therapy at the filing date of Applicant's application would not have read Carling *et al.* to describe such methods, the independent claims are not obvious in view of Carling *et al.*

Claims 14, 15, 17, 18, and 20-29 depend from claim 13; they are therefore patentable over Carling *et al.* for at least the reasons discussed above.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 13-15, 17, 18, 20-29, 34, 36, and 42 under § 103(a).

Claims 16 and 19 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (as applied to claims 13-15, 17, 18, and 20-42) in view of Aberg *et al.* (U.S. Patent 5,795,564) and further in view of Ryrfeldt *et al.* ("Pulmonary disposition of the

potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model," *Biochem. Pharmacol.* 38:17-22, 1989, Abstract). The Examiner states at page 11 of the Office Action that "Carling *et al.* does teach the (R,R) isomer of formoterol set forth in claim 16 and the 22R epimer of budesonide set forth in claim 19." Applicant finds no such teaching in Carling *et al.*, and respectfully requests that the Examiner point out the teaching.

The Office Action also stated at page 12 that

> one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Carling et al. and the (R,R) enantiomer of formoterol and the 22R epimer of budesonide because Aberg et al. and Ryrfeldt et al. teach that these specific isomers possess potent asthmatic effect. The motivation employ the (R,R) isomer of formoterol and 22R epimer of budesonide in the Carling et al. composition is because there is a reasonable expectation of successfully treating asthmatic patients with a more effective medication with reduced adverse effects. *Non-standard English in the original.*

Claims 16 and 19, which depend from claim 13, are patentable for at least the reasons discussed above with respect to claim 13 and the rest of the independent claims. The teachings of Aberg *et al.* and Ryrfeldt *et al.* do not make up for Carling *et al.*'s deficiencies as outlined above, and indeed are cited solely for their teachings concerning specific stereoisomers of the active ingredients. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 16 and 19 under § 103(a).

Applicant believes the claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Extension of Time for three months. Please apply the required fee of $1020, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188002.

Respectfully submitted,

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